

Optimal use of tocilizumab for severe and critical COVID-19 a systematic review and meta-analysis

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SYSTEMATIC REVIEW

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Optimal use of tocilizumab for severe and critical COVID-19: a systematic review and meta-analysis [version 1; peer review: 1 approved, 2 approved with reservations]

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Abstract

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Background: Several studies have revealed the potential use of tocilizumab in treating COVID-19 since no therapy has yet been approved for COVID-19 pneumonia. Tocilizumab may provide clinical benefits for cytokine release syndrome in COVID-19 patients.

Methods: We searched for relevant studies in PubMed, Embase, Medline, and Cochrane published from March to October 2020 to evaluate optimal use and baseline criteria for administration of tocilizumab in severe and critically ill COVID-19 patients. Research involving patients with confirmed SARS-CoV-2 infection, treated with tocilizumab and compared with the standard of care (SOC) was included in this study. We conducted a systematic review to find data about the risks and benefits of tocilizumab and outcomes from different baseline criteria for administration of tocilizumab as a treatment for severe and critically ill COVID-19 patients.

Results: A total of 26 studies, consisting of 23 retrospective studies, one prospective study, and two randomised controlled trials with 2112 patients enrolled in the tocilizumab group and 6160 patients in the SOC group, were included in this meta-analysis. Compared to the SOC, tocilizumab showed benefits for all-cause mortality events and a shorter time until death after first intervention but showed no difference in hospital length of stay. Upon subgroup analysis, tocilizumab showed fewer all-cause mortality events when CRP level

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Open Peer Review

Approval Status

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≥ 100 mg/L, P/F ratio 200-300 mmHg, and P/F ratio < 200 mmHg. However, tocilizumab showed a longer length of stay when CRP < 100 mg/L than the SOC.

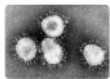
Conclusion: This meta-analysis demonstrated that tocilizumab has a positive effect on all-cause mortality. It should be cautiously administered for optimal results and tailored to the patient's eligibility criteria.

Keywords

Severe, critically ill, COVID-19, tocilizumab



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Introduction

In December 2019, a novel virus named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) that causes Coronavirus Disease-19 (COVID-19) began to spread worldwide and it became a pandemic globally¹. COVID-19 manifestation ranges broadly from mild symptoms to severe illness. Several studies probed multiple types of inflammatory cytokine levels and found higher levels of interleukin (IL)-1 β , IL-1RA, IL-6, IL-7, IL-8, IL-10, IFN- γ , monocyte chemoattractant peptide-1, macrophage inflammatory protein (MIP)-1A, MIP-1B, granulocyte-colony stimulating factor, and tumor necrosis factor-alpha in severe COVID-19 patients^{2,3}. COVID-19 causes severe illness due to activation of the cytokine cascade leading to cytokine release syndrome (CRS), which is delineated by systemic inflammation and multiple organ failure. Therefore, prompt strategies for treating CRS are essential for COVID-19 patients³⁻⁵.

IL-6 is a proinflammatory cytokine that plays an essential role in CRS. Activation and secretion of IL-6 by infected monocytes, macrophages, and dendritic cells cause two main effects; a plethora effect on immune cells and the innate immune system, and increased vascular permeability due to secretion of vascular endothelial growth factor (VEGF), resulting in hypotension and acute respiratory distress syndrome^{3,5,6}.

Tocilizumab, a humanized monoclonal antibody interleukin-6 receptor (IL-6R) inhibitor, is recommended by the National Health Commission of China for treating severe and critically ill patients with elevated IL-6⁷. Recently, several case reports demonstrated tocilizumab could improve the clinical manifestations of seriously ill COVID-19 patients. Several retrospective case-control, single-armed studies and randomized clinical trials declared promising results of tocilizumab treatment in SARS CoV-2 infection. Nevertheless, some systematic reviews and meta-analyses showed an unclear risk of bias and reported debatable results about tocilizumab's benefit as a treatment^{6,8-13}. We performed a systematic review and meta-analysis to research the risks and benefits of tocilizumab and investigate outcomes from different baseline criteria for administration of tocilizumab as a treatment for severe and critically ill COVID-19 patients.

Methods

Study design

We conducted a systematic review and meta-analysis to examine optimal use and baseline criteria for administration of treatment with tocilizumab versus standard of care (SOC) in severe and critically ill COVID-19 patients using data published March to October 2020. All-cause mortality events, length of stay in hospital, and days until death (time to death after first intervention) were measured to determine the risks and benefits of tocilizumab treatment. The baseline criteria for using tocilizumab included physical findings and markers of inflammation such as C-reactive protein (CRP), PaO₂ and FiO₂ ratio (P/F ratio), lactate dehydrogenase (LDH), D-dimer, ferritin, IL-6, leucocyte, lymphocyte count, platelet count, and procalcitonin. We performed screening of several medical databases (PubMed,

Embase, Medline, and Cochrane) to collect data and calculate the risk ratio (RR) and 95% confidence intervals (95% CI). This study used similar methods for the systematic review and meta-analysis to a previous study¹⁴, and was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines accessed from the PRISMA website¹⁵.

Literature search

The search strategy¹⁶, using medical subject headings (MeSH) terms, involved the use of a combination of the following keywords: (tocilizumab) OR (anti-IL-6 monoclonal antibody) OR (IL-6 blockade) OR (IL-6 receptor antagonist) AND severe AND critical ill AND (COVID-19) OR (novel coronavirus disease) OR (SARS-CoV-2). The search was performed by two authors (BAM and CW) in PubMed, Embase, Medline, and Cochrane (March 1st to October 31st 2020, last searched 2nd November 2020) and the language was limited to English. We selected 606 full text and free full text articles from PubMed, included all article types, then we excluded them based on the exclusion criteria of case reports, reviews, editorials, letters, duplicate records, and studies with incomplete data. From filter selection of clinical trials, meta analyses, randomized control trials and systematic reviews within one year we got 42 articles after removing 655 articles (see Figure 1).

Selection criteria

The studies in the three searched databases were included based on the following criteria: (1) patient confirmed for SARS-CoV-2 infection; (2) patients treated with tocilizumab and compared with the SOC; and (3) complete data were provided for clinical outcomes. Exclusion criteria were (1) case reports, reviews, editorials, and letters; (2) duplicate records; and (3) studies with incomplete data.

Data extraction and quality assessment

All articles that qualified for inclusion according to the selection criteria were included in the analysis. Two independent investigators conducted the study assessment (BAM and CW). Two authors (BAM and EA) extracted necessary data from each included study including: first author, publication year, sample size, gender, baseline criteria for administration of tocilizumab, clinical outcomes of tocilizumab group and SOC group. Another consultant resolved any disagreement between the two investigators' findings (ANR and TPA).

The methodological quality assessment

We performed a methodological quality assessment of the article using the Newcastle-Ottawa Scale (NOS) before study inclusion. NOS comprises several items including: patient selection (4 points), comparability of the groups (2 points), and ascertainment of exposure (3 points). Each study was interpreted to be low quality (scores <4), moderate quality (scores of 5–6), or high quality (scores ≥ 7)¹⁷. We only included moderate to high quality articles in the analysis. The study assessment was conducted by two independent investigators (CW and EA) using a pilot form. Another consultant resolved any disagreement between the two investigators' findings (CWN and SDS).

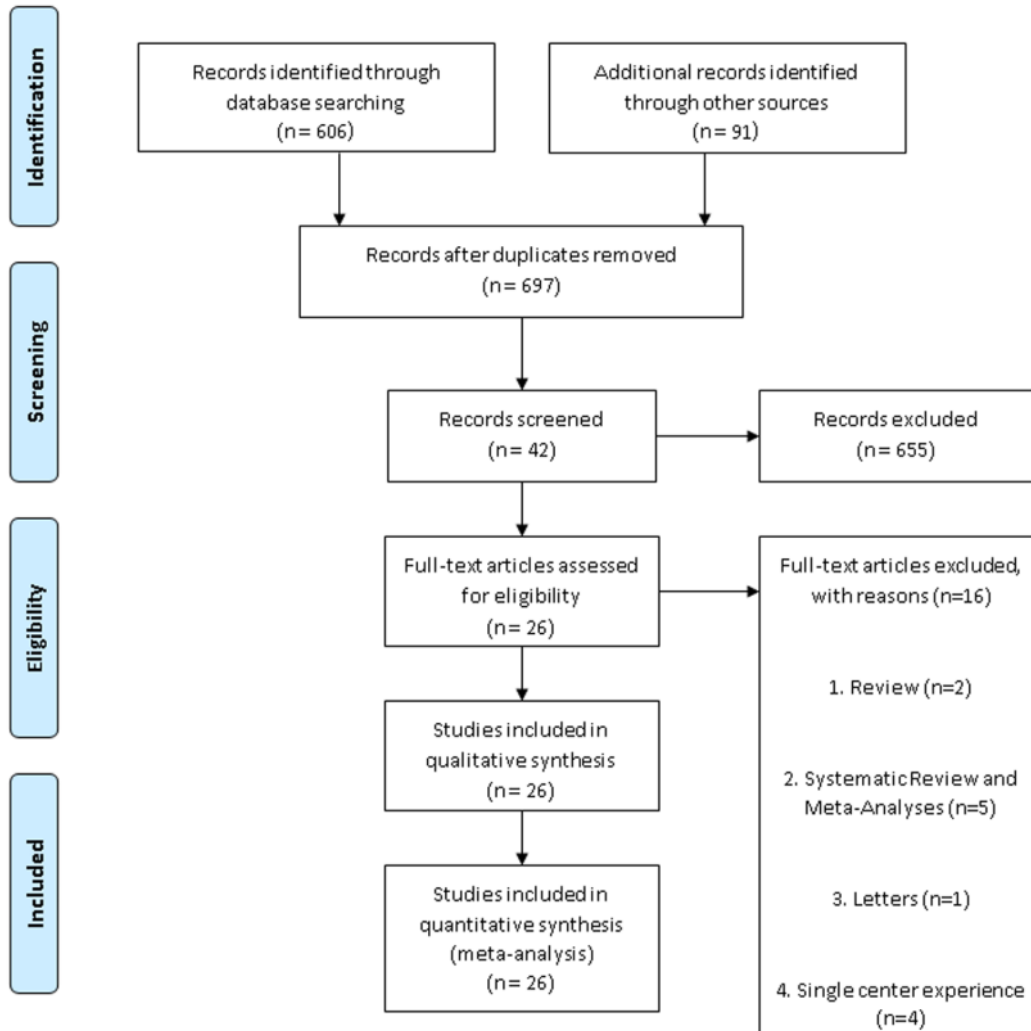


Figure 1. Study selection.

Outcomes

The study outcomes were all-cause mortality events, length of stay in hospital, and days until death (time to death after first intervention), comparing SOC and tocilizumab. We performed subgroup analysis for those outcomes based on CRP level >100 mg/L, CRP level <100 mg/L, PaO₂:FiO₂ ratio (P/F ratio) 200–300 mmHg, and PaO₂:FiO₂ (P/F ratio) <200 mmHg.

Statistical analysis

Data were synthesized using RRs and mean differences (MDs), with 95% CIs. Significance of RRs was determined using the Z test ($p < 0.05$ was considered statistically significant).

They were assessed for heterogeneity and possibility of publication bias before calculating significance. We used the Q test for evaluating the heterogeneity among the included studies. A random effect model was used if heterogeneity existed ($p < 0.10$); if not, a fixed-effect model was adopted. For publication bias, we used Egger's test and a funnel plot ($p < 0.05$ was considered statistically significant).

We analyzed the data with Review Manager (RevMan, Cochrane, London, UK) version 5.4.1. Two authors (BAM and JKF) conducted statistical analysis and presented the results in a forest plot.

Results

Qualifying studies

We obtained 697 qualifying studies, 655 of which were excluded after examining the titles and abstracts. We performed a review of the complete texts for 42 potential studies and 16 studies were then excluded because they were reviews (n=2); systematic review and meta-analyses (n=5); letters (n=1); single-center experiences (n=4); case reports (n=1); brief papers (n=1) or had incomplete data (n=2). Eventually, 26 papers met the inclusion criteria for our meta-analysis; these results are summarized in Figure 1. The characteristics of studies are described in Table 1. We have summarized the results of the outcomes in Table 2.

Outcomes of tocilizumab treatment

There is a significant difference between the SOC group and tocilizumab group (RR: 1.65; 95% CI = 1.37, 2.00) from all-cause mortality events (Figure 2) and days until death (time to death after first intervention) (MD: 6.03; 95% CI: 0.31, 11.76). There is no significant difference between the length of stay (MD: -2.05; 95% CI: -5.25, 1.16). All outcomes showed evidence of heterogeneity and the random effect model was adopted.

Subgroup analysis

There is a significant difference in all-cause mortality events for patients with CRP level >100 mg/L (RR: 1.78; 95% CI: 1.35, 2.34); P/F ratio 200–300 mmHg (RR: 1.84; 95% CI: 1.35, 2.50); and P/F ratio <200 mmHg (RR: 1.44; 95% CI: 1.28, 1.63). For length of stay in hospital, CRP level <100 mg/L showed a significant difference (MD: -7.75; 95% CI: -10.31, -5.20) (Figure 3).

Within the subgroup analysis, evidence of homogeneity was found and we used the fixed effect model for all-cause mortality events for P/F ratio <200 mmHg and length of stay for CRP level \geq 100 mg/L, CRP level <100 mg/L, and P/F ratio 200–300 mmHg. The other parameters were analyzed using the random effect model.

Analysis of publication bias

We assessed the possibility of publication bias using Egger's test. There was no indication of publication bias ($p < 0.05$) for all outcomes.

Discussion

To the best of our knowledge, this is the first meta-analysis investigating the optimal use of tocilizumab in severe and critically ill COVID-19 patients. The 26 studies analysed, mostly retrospective studies with only two clinical trials (Salvarini *et al.* and Somerset *et al.*), suggest that treatment with tocilizumab gives fewer all-cause mortality events than the SOC^{17–42}. Lan *et al.* showed that tocilizumab could not provide additional benefits for clinical outcomes of severe COVID-19, but the mortality rate was lower than the SOC, although this was not

statistically different¹⁰. Studies from Kaye *et al.*, Zhao, J *et al.*, and Zhao, M *et al.*, reported that tocilizumab showed a statistically significant reduction in mortality and fatality than the SOC, similar to our results^{9,11,13}.

Nevertheless, hospital and ICU lengths of stay did not differ between tocilizumab and SOC^{20–26,31,32,35,40,43}. Only one study (Eimer *et al.*) showed that length of stay in hospital on tocilizumab was shorter than the SOC and it was able to shorten the duration of use of a ventilator. However, for the variable days until death, intervention with tocilizumab resulted in a shorter duration until death than the SOC due to secondary infections after tocilizumab treatment³⁰.

Selection criteria from included studies for using tocilizumab treatment for COVID-19 mostly included similar clinical manifestations but baseline laboratory parameters varied. Clinical manifestations for tocilizumab treatment eligibility were frequency of respiration \geq 30 breaths/min and peripheral capillary oxygen saturation (SpO₂) <93% while breathing ambient air. Laboratory markers for tocilizumab treatment eligibility were P/F ratio, CRP, ferritin, LDH and IL-6. In most studies, baseline criteria for administration of tocilizumab were level of CRP \geq 100 mg/L (normal values <6 mg/L), ferritin \geq 900 ng/mL (normal value <400 ng/mL), LDH >220 U/L, and P/R ratio 200–300 mmHg^{18–20,24,36,39,40,42}. However, several studies used baseline criteria for administration of tocilizumab of CRP <100 mg/L and P/F ratio <200 mmHg^{23,30–34,36,43,44}.

The SMACORE study used baseline criteria for administration of tocilizumab of CRP >50 mg/L, procalcitonin <0.5 ng/mL and P/F ratio <300 mmHg in seriously ill COVID-19 patients. Tocilizumab was first administered at 8 mg/kg (up to a maximum 800 mg per dose) intravenously, repeated after 12 hours if no side effects were reported after the first dose. The result from this study was that tocilizumab administration did not reduce mortality rate or ICU admissions²³.

Similar selection criteria were used by Masia *et al.*; the eligible participants had CRP >50 mg/L and tocilizumab was given at an initial dose of 600 mg intravenously for a weight of >75 kg or 400 mg when the weight was <75 kg. If their condition worsened, treatment was reevaluated following 24 hours. A second dose of tocilizumab (400 mg) was given if there was no clinical response. The result from this study was that tocilizumab administration significantly reduced the mortality rate³².

In the randomized trial by Salvarini *et al.*, the selection criteria for tocilizumab treatment were P/F ratio of 200–300 mmHg. Tocilizumab was given intravenously at a starting dose of 8mg/kg until 800 mg within eight hours of randomization, and a second dose administered after 12 hours. This study showed no benefit on disease progression in the tocilizumab group compared with the SOC group⁴².

Table 1. Characteristics and demographics of study.

Article	Study design	Country	Total patients	Mean/median age (years)	TCZ category**	Baseline criteria for TCZ administration	Outcome	NOS
Albertini 2020 ¹⁸	Single-center retrospective observational cohort study	France	44	65 (control) 64 (tocilizumab)	C	CRP ≥ 100mg/L	Clinical and laboratory marker and death	6
Biran 2020 ¹⁹	Retrospective multicentre observational cohort study	USA	764	65 (control) 62 (tocilizumab)	B	CRP ≥ 100 mg/L Ferritin > 900 ng/mL PaO ₂ :FIO ₂ 200-300 mmHg	Hospital-related mortality	8
Campochiaro 2020 ²⁰	Single-center retrospective cohort study	Italy	65	60 (control) 64 (tocilizumab)	B	CRP ≥ 100 mg/L Ferritin > 900 ng/mL LDH > 220 U/L PaO ₂ :FIO ₂ 200-300mmHg	Safety, efficacy	8
Canziani 2020 ²¹	Retrospective case-control study	Italy ²³	128	63 (control) 64 (tocilizumab)	A	CRP ≥ 100mg/L Ferritin >900ng/mL LDH >220 U/L PaO ₂ :FIO ₂ < 200 mmHg	Death	9
Capria 2020 ²²	Retrospective observational case-control study	Italy	85	70 (control) 63 (tocilizumab)	E	PaO ₂ :FIO ₂ 200-300 mmHg	Survival rate	8
Colaneri 2020 ²³	Retrospective case-control study	Italy	112	64 (control) 62 (tocilizumab)	A	CRP >50 mg/L PaO ₂ :FIO ₂ 200- 300mmHg	ICU admission and seven-day mortality rate	8
De Rossi 2020 ²⁴	Retrospective cohort study	Italy	158	71 (control) 62.9 (tocilizumab)	B or D	CRP ≥ 100mg/L LDH > 220 U/L PaO ₂ :FIO ₂ 200-300mmHg	Death and survival rate ¹⁷	7
Eimer 2020 ²⁵	Retrospective cohort study	Sweden	87	58 (control) 29 (tocilizumab)	A	CRP ≥ 100 mg/L	30-day all-cause mortality after admission to ICU	8
Gokhale 2020 ²⁶	Retrospective cohort study ²³	India	161	55 (control) 52 (tocilizumab)	B	PaO ₂ /FIO ₂ < 200mmHg	Death	8
Guaraldi 2020 ²⁷	Retrospective observational cohort study	Italy	544	69 (control) 64 (tocilizumab)	A	PaO ₂ :FIO ₂ 200-300mmHg LDH > 220 U/L	Death or invasive mechanical ventilation	8

Article	Study design	Country	Total patients	Mean/median age (years)	TCZ category**	Baseline criteria for TCZ administration	Outcome	NOS
Gupta 2020 ²⁸	Retrospective multicenter cohort study	USA	4485	63 (control) 58 (tocilizumab)	E	PaO ₂ :FIO ₂ < 200 mmHg	Hazard ratios (HRs), and 30-day mortality, compared via risk differences.	8
Ip 2020 ²⁹	Retrospective observational cohort study	USA	547	69 (control) 62 (tocilizumab)	B	PaO ₂ :FIO ₂ 200-300 mmHg	Death	8
Kewan 2020 ³⁰	Retrospective cohort study	USA	51	70 (control) 62 (tocilizumab)	A	CRP ≥ 100 mg/L Ferritin > 900ng/mL PaO ₂ :FIO ₂ < 200mmHg	Vasopressor support, Status hypoxia, Mortality event	7
Klopfenstein 2020 ³¹	Retrospective case-control study	France	45	71 (control) 77 (tocilizumab)	E	CRP ≥ 100mg/L PaO ₂ :FIO ₂ < 200 mmHg (Ferritin and LDH were mentioned in the eligibility criteria with no exact cut-off point)	Death and/or ICU admissions	9
Masia 2020 ³²	A prospective cohort study	Spain	138	68 (control) 62 (tocilizumab)	C	CRP < 100 mg/L Ferritin < 900ng/mL	Death, viral kinetics and antibody response	9
Mikulska 2020 ³³	Retrospective observational single-center case-control study	Italy	196	73.5 (control) 64.5 (tocilizumab)	A	CRP > 50 mg/L Ferritin > 900ng/mL PaO ₂ :FIO ₂ 200- 300 mmHg	Failure-free survival	7
Moreno-Perez 2020 ³⁴	Retrospective cohort study	Spain	236	57 (control) 62 (tocilizumab)	C	CRP > 50mg/L Ferritin > 1000ng/mL LDH > 300U/L PaO ₂ :FIO ₂ 200-300mmHg	All-cause mortality	8
Patel 2020 ³⁵	Retrospective cohort study	Sweden	83	41 (control) 42 (tocilizumab)	E	CRP < 100 mg/L PaO ₂ : FIO ₂ <200 mmHg	Death	8
Potere 2020 ³⁶	Retrospective case-control study	Italy	80	54 (control) 56 (tocilizumab)	D	CRP ≥ 100mg/L PaO ₂ :FIO ₂ 200-300 mmHg	Requirement of invasive mechanical ventilation or death	8
Quartuccio 2020 ³⁷	Retrospective single-center case-control study	Italy	111	56.2 (control) 62.4 (tocilizumab)	A	CRP < 100mg/L LDH > 220U/L	Death	9

Article	Study design	Country	Total patients	Mean/median age (years)	TCZ category**	Baseline criteria for TCZ administration	Outcome	NOS
Ramiro 2020 ³⁹	Retrospective case-control single-center study	Netherlands	86	67 (control) 67 (tocilizumab)	A	CRP ≥ 100mg/L Ferritin > 900ng/mL PaO2:FIO2 200-300 mmHg	Discharge from the hospital or improvement compared with baseline	9
Ramaswamy 2020 ⁴⁰	A case-control study	USA	86	21 (control) 65 (tocilizumab)	B	CRP > 70mg/L PaO2:FIO2 200-300 mmHg	Mortality event	6
Rojas-Martel 2020 ⁴¹	Retrospective single-center study	USA	193	62 (control) 59 (tocilizumab)	No detail was reported	CRP ≥ 100mg/L Ferritin > 900ng/L PaO2:FIO2 200-300 mmHg	Overall mortality rate	7
Rossotti 2020 ⁴²	Retrospective case-control study	Italy	222	59 (control) 59 (tocilizumab)	A	PaO2:FIO2 200-300mmHg	Overall survival analysis	8
Salvarini 2020 ⁴³	Randomized controlled trial	USA	126	60 (control) 61.5 (tocilizumab)	A	CRP ≥ 100mg/dL PaO2:FIO2 200-300 mmHg Ferritin < 900ng/L	intensive care unit with invasivemechanicalventilation, deathfromall causes, or clinical aggravation	7
Somers 2020 ⁴⁴	Randomized controlled trial	USA	154	60 (control) 55 (tocilizumab)	A	CRP ≥ 100mg/L Ferritin > 900ng/L PaO2:FIO2 < 200mmHg LDH > 220U/L	Survival probability after intubation	6

**The dose and administration of tocilizumab are grouped into:

- a. Category A: Intravenous Tocilizumab 8mg/kg bb up to 800 mg, added by a second dose after 12-24 hours
- b. Category B: Single dose intravenous Tocilizumab 400mg
- c. Category C: Single dose intravenous Tocilizumab 600mg
- d. Category D: 324 mg of Subcutaneous injections of tocilizumab
- e. Category E: not classified

TCZ, tocilizumab; NOS, Newcastle-Ottawa Scale; CRP, C-reactive protein; LDH, lactate dehydrogenase; ICU, intensive care unit.

Table 2. Outcome and laboratory marker Tocilizumab group and standard of care group.

Outcomes	N	Mode	Value				pE	pHet	P	RR	95% CI
			SOC		TCZ						
			n	Total	n	Total					
All-cause mortality	26	Random	2475	61160	523	2112	0.2500	<0.00001	<0.00001	1.65	1.37, 2.00
Subgroup Analysis											
CRP >100 mg/L	13	Random	508	1114	234	894	0.1400	0.001	<0.0001	1.71	1.30, 2.24
CRP < 100 mg/L	7	Random	83	512	28	266	0.4500	<0.0001	0.8900	1.19	0.39, 3.59
P/F ratio 200–300 mmHg	15	Random	880	2137	296	1208	0.1300	<0.00001	0.0001	1.84	1.35, 2.50
P/F ratio <200 mmHg	8	Fixed	1576	3829	220	722	0.6600	0.8400	<0.00001	1.44	1.28, 1.63
	N	Mode	Value				pE	pHet	P	MD	95% CI
			SOC		TCZ						
			n	Total	n	Total					
Length of stay (d)	11	Random	14.22±3.21		16.81±2.25		0.5300	<0.00001	0.21	-2.05	-5.25, 1.16
Subgroup Analysis											
CRP >100 mg/L	8	Fixed	16.02±3.86		16.35±3.19		0.4800	0.7300	0.18	1.17	-0.54, 2.88
CRP < 100 mg/L	3	Fixed	10.17±1.97		18.77±1.18		0.8500	0.8700	<0.00001	-7.75	-10.31, -5.20
P/F ratio 200–300 mmHg	3	Fixed	14.28±2.73		14.28±1.53		0.8800	0.3700	0.30	1.15	-1.02, 3.31
P/F ratio < 200 mmHg	7	Random	15.36±5.73		18.74±2.23		0.7300	0.0007	0.33	-2.38	-7.19, 2.44
Days of death (d)	4	Random	13.32±3.33		6.89±6.52		0.1200	<0.00001	0.04	6.03	0.31, 11.76

Note, data were presents as mean ± SD or n [%], SOC, Standard of care; TCZ, tocilizumab; N, number of studies; CRP, C-reactive protein; RR, relative risk; MD, mean difference; pE, p Egger; PHet, p Heterogeneity; CI, confidence interval.

According to the Moreno-Perez study, candidates for tocilizumab treatment had poor prognostic factors or worsening disease. One of indication for worsening condition was CRP level >100 mg/L or P/F ratio <200 mmHg³⁴.

Our subgroup analysis showed tocilizumab had a good result when CRP levels were ≥100 mg/L and P/F ratio was 200–300 mmHg or <200 mmHg. Administration of tocilizumab for CRP levels <100 mg/L did not reduce mortality and showed a longer length of stay in hospital.

There are various types of administration of tocilizumab treatment among studies. Tocilizumab can be administrated at a low dose (400 mg or 4 mg/kg) or high dose (800 mg or 8 mg/kg), as a single-dose and then continue with the second dose if clinical condition worsens in 24 hours (maximum 800 mg per dose), intravenously or subcutaneously.

Strengths and limitations of the analysis

Meta-analysis on this topic has not been previously conducted; only mortality events and ICU admissions have been reported by previous studies^{9–11,13}. In our study, we evaluate all-cause

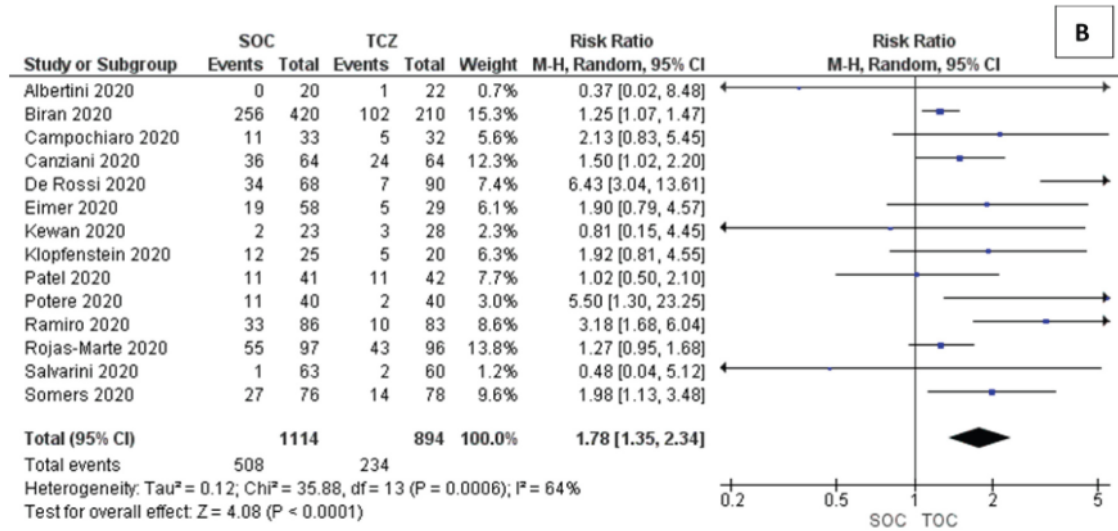
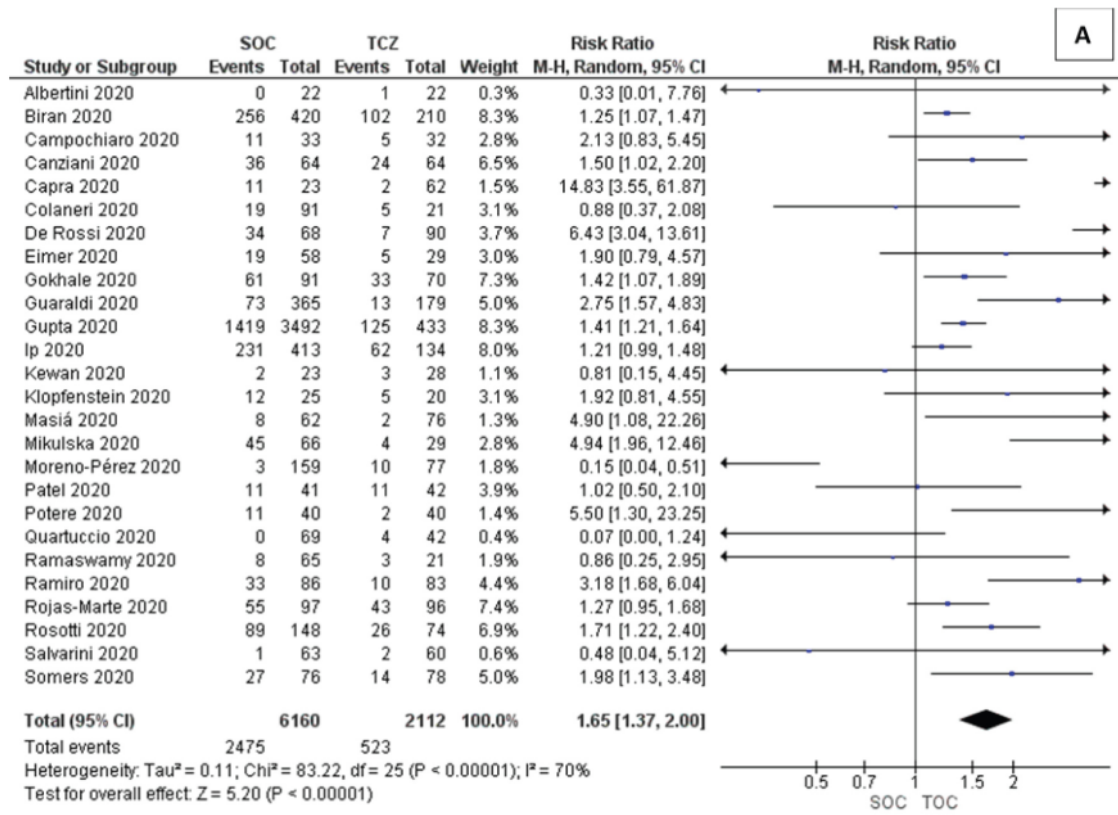
mortality events, length of stay in hospital, and days until death (time to death after first intervention) and carry out subgroup analysis of baseline criteria for administration of tocilizumab treatment. This study has a larger sample size; 2112 patients in the tocilizumab group and 6160 patients in the SOC group.

The limitations of this study are that we didn't perform subgroup analysis of baseline criteria for administration of tocilizumab and didn't analyze secondary outcomes after tocilizumab treatment like bacterial or fungal infections, thrombotic events, major bleeding, or requirement of invasive mechanical ventilation requirement. The results of our study should be used carefully because most studies included were retrospective and only two were randomized clinical trials, since it has been difficult to perform randomized trial during this pandemic. A meta-analysis of more clinical trial data will provide a more precise result for tocilizumab treatment in severe and critically ill COVID-19 patients.

Conclusion

Our study provides meaningful data regarding the effect of tocilizumab in severe and critically ill confirmed COVID-19

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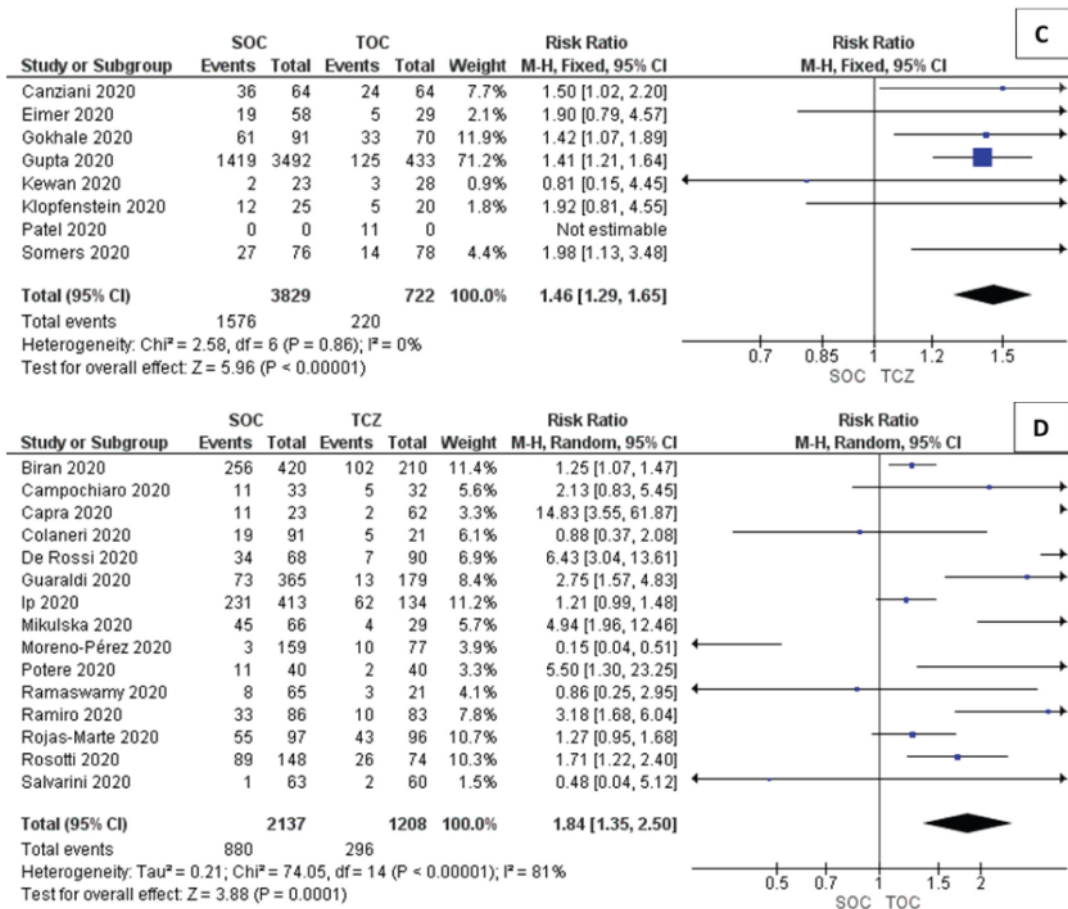


Figure 2. Forest plot outcome between SOC group and TCZ group. A) All-cause mortality event; **B)** Subgroup CRP >100 mg/L; **C)** Subgroup PaO₂:FiO₂ 200-300 mmHg; **D)** Subgroup PaO₂:FiO₂ <200 mmHg. SOC, standard of care; TCZ, tocilizumab; CRP, C-reactive protein; SD, standard deviation; CI, confidence intervals.

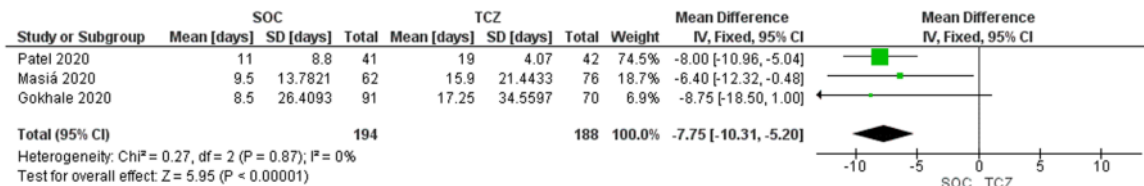


Figure 3. A forest plot length of stay baseline criteria for administration of tocilizumab CRP < 100 mg/L. SOC, standard of care; TCZ, tocilizumab; CRP, C-reactive protein; SD, standard deviation; CI, confidence intervals.

patients. Tocilizumab is a treatment option for severe and critically ill COVID-19 patients and it appears to reduce mortality events, especially when CRP level >100 mg/L, P/F ratio

200–300 mmHg, and P/F ratio <200 mmHg. However, tocilizumab should be used cautiously according to proper selection criteria to achieve optimal results and its use should be tailored

according to the eligibility of the patients. Further studies are still required, especially regarding optimal dosage and administration route of tocilizumab in COVID-19 patients.

Data availability

Underlying data

Figshare: Data systematic review and meta-analysis optimal use tocilizumab.zip. <https://doi.org/10.6084/m9.figshare.13655894.v1>¹⁶.

This project contains the following underlying data:

- TCZ_for_COVID-19.csv9

Extended data

Figshare: Data systematic review and meta-analysis optimal use tocilizumab.zip. <https://doi.org/10.6084/m9.figshare.13655894.v1>¹⁶.

This project contains the following extended data:

- PubMed and Cochrane search strategies (in JPG format)

Reporting guidelines

Figshare: PRISMA checklist for “Optimal use of tocilizumab for severe and critical COVID-19: a systematic review and meta-analysis”. <https://doi.org/10.6084/m9.figshare.13655894.v1>¹⁶.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Acknowledgments

We are here to thank Prof. Dr. dr. Nasronudin, Sp. PD K-PTI for supporting us in completing this study.

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 **Zhongheng Zhang** 

Department of Emergency Medicine, Sir Run Run Shaw Hospital, Zhejiang, China

This meta-analysis can provide updated evidence for an important clinical question; However, I have several comments:

1. The authors combined evidence from RCT and observational studies, which is not appropriate; the authors need to at least perform subgroup (sensitivity) analysis by restricting only high-quality trials.
2. Bayesian meta-analysis may be appropriate for down-weighting observational studies.
3. Most studies are small in sample size; the limitation of small study effect should be addressed and discussed; this effect has been well characterized in literature (Zhang *et al.*, 2013¹).
4. Many observational studies may include adjusted effect size, try to combine this adjusted OR (RR) and to see whether this will change the current conclusion.
5. Many interventional meta-analysis on COVID-19 have been published in the literature (Kim *et al.*, 2020², Aziz *et al.*, 2021³, Zhao *et al.*, 2020⁴ and Kotak *et al.*, 2020⁵); the authors need to clarify how their study can add to the existing literature.

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Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: critical care medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Mar 2021

Satriyo Dwi Suryantoro, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

We would like to firstly express our gratitude for having our manuscript reviewed thoroughly.

Best regards,

Research team.

Competing Interests: We have no conflict of interest

Reviewer Report 02 March 2021

<https://doi.org/10.5256/f1000research.48118.r79722>

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**Wiwien Heru Wiyono**

Department of Pulmonology and Respiratory Medicine, Universitas Indonesia, Jakarta, Indonesia

1) Data extraction and quality assessment:

Two independent investigators conducted the study assessment (BAM and CW). Two authors (BAM and EA) extracted necessary data.

I think it is not necessary to inform that one acts as an independent investigator, while he is also a member of the authors who extracted the data. Its independence is questionable.

2) Conclusion:

Tocilizumab is a treatment option for severe and critically ill COVID-19 patients and it appears to reduce mortality events, especially when CRP level >100 mg/L, P/F ratio 200–300 mmHg, and P/F ratio < 200 mmHg.

1. The authors did not explain in the discussion that P/F ratio 200-300 mmHg and P/F ratio < 200 mmHg is actually different in mode.
2. When the mode of both variables is ignored, why not just conclude: when P/F ratio < 300 mm Hg.
3. Clinicians need clear conclusions, the authors' conclusions about P/F ratio 200-300 mmHg and P/F ratio < 200mm Hg are confusing.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Pulmonology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Mar 2021

Satriyo Dwi Suryantoro, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

Dear Prof. Wiwien,

1) Thank you for the helpful and considerate advices.

2) To all intents and purposes, in this research we didn't particularly examine and conclude the effect of TCZ on P/F ratio less than 300, yet we figured out significantly good impact/effect of TCZ on patients with mild ARDS (P/F ratio 200-300 mmHg), as we have mentioned on page 9 of the manuscript.

Competing Interests: There is no financial competing interest. We hope to benefit as a result of our submission for further treatment COVID-19 using Tocilizumab.

Reviewer Report 05 February 2021

<https://doi.org/10.5256/f1000research.48118.r78921>

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Lorenzo Cosmi

Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

The manuscript "Optimal use of tocilizumab for severe and critical COVID-19: a systematic review and meta-analysis", is an exhaustive meta-analysis on studies that have evaluated the efficacy of treatment with tocilizumab in COVID-19. The meta-analysis is well performed, and the results are convincing and in line with the real life evidences, which suggest an efficacy of such a treatment in selected patients. The authors correctly underline that the treatment works in patients with high inflammatory status and with impairment of respiratory function (P/F ratio below than 300 mm Hg). The concept that tocilizumab improves the prognosis of severe COVID-19 patients, reducing hyper inflammation that contributes to vascular pulmonary damage is an important message for the scientific community.

I have no particular concerns on this manuscript. I only suggest to quote in the introduction also a recent paper that focuses on the ability of tocilizumab to improve the lung perfusion in these patients (Salvati *et al.*, 2020¹).

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: COVID-19

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